YOU'VE COME A LONG WAY, BABY: OR HAVE YOU?

Long-Term Prognosis in Children with Neonatal Seizures: A Population-Based Study. Ronen GM, Buckley D, Penney S, Streiner DL. *Neurology* 2007;69(19):1816–1822. OBJECTIVE: To examine outcome and explore for prognostic markers in a cohort <10 years following neonatal seizures. METHODS: We prospectively diagnosed clinical neonatal seizures with high specificity for true epileptic seizures in a population-based setting of all live newborns in the province of Newfoundland, Canada, between 1990 and 1995. Children with neonatal seizures were followed by specialized provincial health services. Follow-up data were collected on epilepsy, physical and cognitive impairments, and other heath issues. RESULTS: Data were available on 82 out of 90 subjects. We added information on six others whose outcome was clearly predictable from earlier information. Prognosis was better for term than for preterm infants ($p = 0.003$): term: 28 (45%) normal, 10 (16%) deaths, and 24 (39%) with impairments; preterm: 3 (12%) normal, 11 (42%) deaths, and 12 (46%) with impairments. Of survivors, 17 (27%) developed epilepsy, 16 (25%) had cerebral palsy, 13 (20%) had mental retardation, and 17 (27%) had learning disorders. Variables associated with poor prognosis were Sarnat stage III or equivalent severe encephalopathy, cerebral dysgenesis, complicated intraventricular hemorrhage, infections in the preterm infants, abnormal neonatal EEGs, and the need for multiple drugs to treat the neonatal seizures. Pure clonic seizures without facial involvement in term infants suggested favorable outcome, whereas generalized myoclonic seizures in preterm infants were associated with mortality. CONCLUSIONS: Poor prognosis for premature infants with seizures is reflected in high rates of subsequent long-term disability and mortality. The severity and timing of the pathologic process continue to be the major determinants for outcome.

Gestational Age, Birth Weight, Intrauterine Growth, and the Risk of Epilepsy. Sun Y, Vestergaard M, Pedersen CB, Christensen J, Basso O, Olsen J. *Am J Epidemiol* 2008;167(3):262–270. The authors evaluated the association between gestational age, birth weight, intrauterine growth, and epilepsy in a population-based cohort of 1.4 million singletons born in Denmark (1979–2002). A total of 14,334 inpatients (1979–2002) and outpatients (1995–2002) with epilepsy were registered in the Danish National Hospital Register. Children who were potentially growth restricted were identified through two methods: 1) sex-, birth-order-, and gestational-age-specific *z* score of birth weight; and 2) deviation from the expected birth weight estimated based on the birth weight of an older sibling. The incidence rates of epilepsy increased consistently with decreasing gestational age and birth weight. The incidence rate ratios of epilepsy in the first year of life were more than fivefold among children born at 22–32 weeks compared with 39–41 weeks and among children whose birth weight was <2,000 g compared with 3,000–3,999 g. The association was modified by age but remained into early adulthood. Incidence rate ratios of epilepsy were increased among children identified as growth restricted according to either of the two methods. In conclusion, short gestational age, low birth weight, and intrauterine growth restriction are associated with an increased risk of epilepsy.

COMMENTARY

When the National Collaborative Perinatal Project (NCPP) published the results of their prospective follow-up of 54,000 pregnancies occurring between 1959 and 1966, important information about neonatal seizures and the outcomes experienced by these children were obtained. In that study, neonatal seizures occurred in 277 children (0.5%), with a mortality rate of 34.8% (1). At the 7-year follow-up, 70% of the survivors were normal. However, among these survivors, epilepsy was the most common neurologic sequelae: 22% of patients had one or more afebrile seizures compared with a rate of 0.9% in the NCPP population as a whole. The data clearly showed that in the neonatal seizure group, there was a significant increase in the number of babies who were born at <2,500 g in weight and <36 weeks gestation ($p < 0.001$). A companion paper examined the factors that predicted death, mental retardation, cerebral palsy, and epilepsy; it concluded that neonatal seizures (and/or their duration) may be a better indicator of the severity of intrauterine stress than the Apgar score (2).

This background provides a basis for a reexamination of the situation among babies born almost 30 years later. The NCPP data provided a perspective that informed many of the ensuing attempts to understand and characterize neonatal seizures more fully, in the hope that better interventions would lead to better outcomes. The Ronen et al. study reviewed here suggests that these hopes have not been realized. Although neonatal seizures

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were less frequent (0.26%) than in the initial (NCPP) study, the finding may simply reflect more rigid "entry" criteria and fewer hypocalcemic seizures, as these seizures are currently prevented and managed far better. Death has been somewhat averted; however, there does not appear to be an increase in normal outcomes, with epilepsy occurring in 34% of all births and 48% of premature infants. Epilepsy that follows neonatal seizures may be particularly problematic, as the risk of infantile spasms in this group is 100 times the normal population. A question that always arises with studies from different eras is whether the comparison is actually among apples and oranges. The populations differed significantly, and certainly more premature babies are kept alive today than were 40 years ago.

Of note in the Ronen et al. paper is that the number of seizures did not correlate with outcome, but the type of seizures did. Premature babies with myoclonic seizures had a particularly high mortality. Continuing controversy exists with respect to whether particular seizure types correlate with poorer outcome, and if so, why? Is it because, as Lombroso suggests (3), that these infants have experienced more severe CNS insults—reflected by the inability to detect EEG changes embedded in very abnormal background activity? The severity of the underlying disorder (e.g., encephalopathy) as well as the period of development in which it occurs influences outcome. Brunquell et al. similarly reported that clinical semiology was predictive of outcome and asserted that unique pathophysiologic processes underlie the different seizure types (4). The authors speculated that understanding these relationships might well lead to improved interventions.

In the past few decades, neuroscience has continued to probe the unique aspects of neonatal seizures. Recognizing the unique role of $GABA_A$ receptors in neonates, Dzhala and colleagues (reviewed in the Basic Science section of this issue) have demonstrated enhanced phenobarbital efficacy with the use of bumetanide that blocks the NKCC1 transporter and alters $Cl^=$ flux (5). Similarly, Sankar and Rho emphasize the detrimental effects of prolonged seizures on brain plasticity on the developing brain (6). Finally, Lombroso questions whether neonatal seizures "plant the roots for epileptogenesis and cause long-term deficits" (7). Lombroso concludes that there is no convincing evidence that the seizures themselves produce epileptogenesis, but rather that they are the marker of the underlying problem. This assertion does not mean that the outcome of the underlying etiology (often hypoxia-ischemia) is immutable.

Although the paper by Sun and colleagues, reviewed here, does not deal with neonatal seizures, it provides further information about the vulnerability of the newborn and examines some of the factors associated with developing epilepsy. In this population-based study in which children were followed for up to 24 years, a crude incidence rate of epilepsy of 92.6 in 100,000 is provided. The incidence rate of epilepsy was associated with decreasing gestational age and intrauterine growth restriction. Thus, it may be of value to examine again the reasons for premature delivery—reassessing the causal roles of the intrauterine environment and fetal health in the development of neonatal seizures. The immature brain of a premature child is disadvantaged and susceptible to further insults, making it more difficult to successfully achieve developmental processes critical to normal outcome. A somewhat similar, recent population-based study from Nova Scotia again found neonatal seizures to be a most important risk factor for development of epilepsy and went so far as to suggest that: "if no infants were born small for gestational age, then 7.4% of epilepsy would be prevented (assuming causality)" (8). There is always a caveat!

Researchers and clinicians have come a long way in helping vulnerable newborns survive; however, many challenges lay ahead. The possibilities of strategies (e.g., hypothermia, novel anticonvulsants, or neuroprotective agents) to treat neonates with seizures are alluring (9), but we have a long way to go.

by Eileen P.G. Vining, MD

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Of Race, Ethnicity, and Rash: The Genetics of Antiepileptic Drug-Induced Skin Reactions

Association between HLA-B*1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. *Epilepsia* 2007;48(5):1015–1018. A previous study conducted in Taiwan found a 100% association between HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome (SJS) in Han Chinese subjects, with an extremely high odds ratio compared with carbamazepine-tolerant subjects (odds ratio = 2,504). We examined this association in 24 Hong Kong Han Chinese subjects who had cutaneous adverse reactions induced by different antiepileptic drugs (AEDs). They were matched with 48 AED-tolerant controls. HLA-B*1502 was associated with severe cutaneous reactions (SCR) induced by AEDs, which included carbamazepine, phenytoin, and lamotrigine ($p = 0.001$, odds ratio = 17.6), but was not associated with maculopapular exanthema (MPE) ($p = 0.32$). Further studies in larger samples of ethnically matched subjects should be conducted to confirm the findings. Identification of genetic polymorphisms predisposing to development of AED-induced SCR offers the possibility of avoiding these high-risk drugs in genetically susceptible individuals.

COMMENTARY

Serious allergic cutaneous reactions, especially Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are among the most feared complications of antiepileptic drug (AED) therapy. SJS and TEN are characterized by a blistering exanthema with mucosal involvement and skin detachment. TEN is defined by more extensive skin involvement than SJS (>30%) and has a higher mortality rate, 25% or more. The risk of these rare conditions colors many epilepsy treatment decisions, influencing the choice of an AED and the speed at which it is initiated. For this reason, the emerging evidence that genetic factors strongly predict occurrence of SJS and TEN will most certainly lead to changes in clinical practice.

SJS/TEN is reportedly two to three times more prevalent in Han Chinese than Caucasians (1), with carbamazepine use associated with 25 to 33% of cases for Asians (2) compared with 5–6% for Europeans (3). These differences have now been explained by demonstration of a close association between the two conditions and the human leukocyte antigen, *HLA-B*1502* (2,4). The most comprehensive study found that 59 of 60 Han Chinese patients in Taiwan with carbamazepine-induced SJS or TEN had the *HLA-B*1502* allele, as compared with 6 of 144 control subjects and 1 of 31 patients with carbamazepine-induced maculopapular eruption (MPE) or hypersensitivity syndrome (HSS, defined as a rash accompanied by multiorgan involvement, such as hepatitis and nephritis, and systemic symptoms, such as fever and arthralgias) (4).

The SJS/TEN susceptibility locus maps tightly to the region of the *HLA-B* gene (4). The strong linkage suggests that the product of this gene may have a direct functional role in drug hypersensitivity. It has been proposed that the *HLA-B*1502* allele codes for a molecule that is displayed on the surface of antigen-presenting cells (5). Carbamazepine or a metabolite, combined with an unknown peptide, binds to this molecule, which then activates naive CD8+ T lymphocytes that, in turn, proliferate, leading to SJS/TEN. The lack of association between carbamazepine-induced MPE/HSS and *HLA-B*1502* suggests that it may be mediated by somewhat different immune mechanisms than SJS/TEN.

*HLA-B*1502* has a strikingly variable occurrence among different ethnic groups, which has been only partially defined. It occurs in 10–15% of individuals from southern China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan (6) and has a prevalence rate of 2–4%, or higher, in other southern Asian groups, including Indians. It is uncommon in Japan and Korea (<1%) (6) and in European Caucasians (0–0.1%) (5). Remarkably, one study of 12 French and German patients with carbamazepine-induced SJS/TEN found that all 4 *HLA-B*1502*-positive individuals had Asian ancestry.

Other *HLA-B* alleles have been shown to predispose patients to different hypersensitivity reactions to drugs other than carbamazepine (5). For instance, *HLA-B*5801* is strongly predictive of SJS/TEN/HSS from allopurinol (5); this allele is found in most populations but is more prevalent in Asian Indians (3–15%) and Chinese (8.8–10.9%). Similarly, *HLA-B*5701* predicts MPE/HSS to abacavir in Caucasians but not patients of African or Hispanic descent.

The work by Man et al. offers strong confirmation of the earlier reports from Taiwan (1,4), with *HLA-B*1502* being found in 6 of 6 SJS/TEN cases, 2 of 18 MPE/HSS cases, and 7 of 48 control subjects. However, new concerns are raised as the *HLA-B*1502*-positive SJS/TEN group included two patients not exposed to carbamazepine, one having been started on phenytoin and the other on lamotrigine. Unfortunately, the true risk of phenytoin and lamotrigine exposure in *HLA-B*1502*-positive patients cannot be deduced from single cases.

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A recent FDA alert recommends that patients with ancestry from at-risk populations be screened for the *HLA-B* 1502* allele prior to starting carbamazepine and that positive patients not be exposed to it (6). The feasibility and benefits of *HLA-B* 5701* screening for abacavir have already been well documented (7). Although a cost–benefit analysis is not yet available for genetic screening for carbamazepine hypersensitivity, the arguments for performing it are compelling in high-risk populations, considering the severe consequences of SJS/TEN and the fact that high-resolution HLA-B screening for B*1502 should cost approximately $200 in the United States and would delay drug initiation by only 1–2 days.

Although genetic screening is a promising method to predict and reduce occurrence of carbamazepine-induced severe cutaneous reactions, major uncertainties remain that make it difficult for the clinician to apply this new tool with confidence. What is the prevalence of the *HLA-B* 1502* allele in patients with African, Middle Eastern, Hispanic, and Native American ancestry? What is the risk of SJS/TEN when *HLA-B* 1502*-positive patients are started on other AEDs such as lamotrigine, or phenytoin? Are there additional, undiscovered, strong predictors of AED hypersensitivity for other ethnic groups? These questions can be addressed by further studies using current methods. The answers will lead to safer treatment of epilepsy.

by John W. Miller, MD, PhD

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Outcomes Remain Ambivalent for Deep Brain Stimulation and Epilepsy

Deep Brain Stimulation in Patients with Refractory Temporal Lobe Epilepsy. Boon P, Vonck K, De Herdt V, Van Dycke A, Goethals M, Goossens L, Van Zandijcke M, De Smedt T, Dewaele I, Achten R, Wadman W, Dewaele F, Caemaert J, Van Roost D. *Epilepsia* 2007;48(8):1551–1560. PURPOSE: This pilot study prospectively evaluated the efficacy of long-term deep brain stimulation (DBS) in medial temporal lobe (MTL) structures in patients with MTL epilepsy. METHODS: Twelve consecutive patients with refractory MTL epilepsy were included in this study. The protocol included invasive video-EEG monitoring for ictal-onset localization and evaluation for subsequent stimulation of the ictal-onset zone. Side effects and changes in seizure frequency were carefully monitored. RESULTS: Ten of 12 patients underwent long-term MTL DBS. Two of 12 patients underwent selective amygdalohippocampectomy. After mean follow-up of 31 months (range, 12–52 months), one of 10 stimulated patients are seizure-free (>1 year), one of 10 patients had a >90% reduction in seizure frequency; five of 10 patients had a seizure-frequency reduction of ≥50%; two of 10 patients had a seizure-frequency reduction of 30–49%; and one of 10 patients was a nonresponder. None of the patients reported side effects. In one patient, MRI showed asymptomatic intracranial hemorrhages along the trajectory of the DBS electrodes. None of the patients showed changes in clinical neurological testing. Patients who underwent selective amygdalohippocampectomy are seizure-free (>1 year), AEDs are unchanged, and no side effects have occurred. CONCLUSIONS: This open pilot study demonstrates the potential efficacy of long-term DBS in MTL structures that should now be further confirmed by multicenter randomized controlled trials.

COMMENTARY

Neurostimulation is a technique used in many areas of neurology. Based on adequate clinical trials, deep brain

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stimulation (DBS) is an accepted and proven technique for disorders such as tremor, movement disorder, and even pain (1). DBS also has been evaluated for epilepsy but still is not accepted as a routine treatment modality. The most salient reasons for the infrequent use of DBS for patients with epilepsy are because there is no consensus regarding the location of optimal stimulation sites and for which specific seizure types it is most effective. Current, ongoing studies, which have not yet been reported in full, involve the seizure focus and the thalamus (2–4). Even within the thalamus, it is not clear whether the centromedial nucleus or the anterior nucleus is the best site for DBS. There is some evidence that DBS for epilepsy also may be effective at the subthalamic nucleus, the caudate nucleus, and the cerebellum (2). The cerebellum actually was the first site to undergo DBS experimentation, but so far the results of small studies are not encouraging (5) and many trials were designed with so few patients that no reliable conclusions can be made (6).

In the Boon et al. study, stimulation was given intermittently over 24 hours, irrespective of seizure activity at the seizure site. In other words, a vagus nerve stimulation-like paradigm was employed, but the stimulation was applied locally instead of from a distant site. The patients participating in the study had mesial temporal lobe foci and were undergoing epilepsy surgery evaluation. All the patients had been implanted with electrodes for the surgical evaluation, so they were ethically appropriate subjects to recruit for an efficacy study of this methodology. Furthermore, patients were made aware of the fact that DBS was being administered.

Three patients, who had previously been reported on, served as the rationale for further evaluating the technique, as they all had done well with focal DBS (7). Backed by the initial success, the authors intended to implant 12 additional patients with stimulating electrodes. The inclusion criteria for these patients were: 1) suspicion of a mesial temporal focus on the basis of video-EEG monitoring, 2) at least one complex partial seizure monthly in spite of taking at least two antiepileptic drugs (AEDs), and 3) incongruent findings among other evaluations to localize the seizure focus, requiring invasive video-EEG monitoring in the bilateral medial temporal lobes and other subdural areas. In addition to the other electrode grids that were required for surgical evaluation, two quadrupolar electrodes for DBS were placed in each hemisphere through two parietooccipital burrholes—one in the amygdala and one in the anterior part of the hippocampus. All electrode grids and DBS electrodes were implanted during the same surgery.

After 48 hours of video-EEG monitoring, the AEDs were downtitrated until the patient's habitual seizures appeared. If there was evidence of a focal or regional or bilateral mesial temporal ictus, then the patient was offered a trial of continuous DBS; all 12 patients initially consented to be in the study. If only one temporal lobe had an ictal focus, then the patients were offered unilateral DBS. If both temporal lobes had ictal foci, then bilateral DBS was offered. If spikes on the EEG were reduced by 50% after stimulation for 7 days with an external stimulator, compared with the condition during video EEG with AED taper, then the external DBS generator was permanently implanted in the abdominal area. If there was not a 50% reduction in spikes after a week of stimulation, the external stimulation was continued for another 21 days. If the number of spikes were still not reduced by >50%, then another 3 weeks of acute stimulation was allowed, with adjusted stimulation frequency. At that point, if a >50% spike reduction was still not achieved, then the patient was offered resective surgery or a continuation of the AED treatment. There were 2 patients among the 12 who went on to have epilepsy surgery; they both subsequently became seizure-free. One of the two patients had a right-sided focal ictal onset and went immediately into surgery, without ever trying DBS. The other patient attempted DBS, but the ictal spikes were not reduced by 50% after 6 weeks of treatment. The other 10 patients had a generator implanted, as they fulfilled the criteria for chronic implantation.

The results for the patients given DBS are mediocre, with only one who became seizure-free and one who had a 90% seizure reduction. The level of seizure reduction overall was very similar to that seen in vagus nerve stimulation trials or when adding an experimental AED. Side effects were few and minor, except one patient who was administered DBS and had asymptomatic hemorrhagic bleeding.

Unfortunately, the lack of a placebo group affects the reliability of the study's outcomes, and a run-in placebo period would have been helpful to cull out placebo responders. Even the major criterion for stimulation—spike reduction by over 50%—is a totally unproven method for selecting responders and would have benefited from a placebo run-in. For patients with an inoperable epileptic focus, DBS might be an alternative. Yet, if vagus nerve stimulation produces efficacy similar to DBS, why should invasive implantation of electrodes in the brain be performed, when the same result using peripheral stimulation might suffice? However, considering the increasing number of applications of DBS for neurological diseases, it may be important to continue exploring DBS for epilepsy treatment but with more solid study design.

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THALAMUS: THE "INNER CHAMBER" REVEALS ITS SECRETS

A Subcortical Network of Dysfunction in TLE Measured by Magnetic Resonance Spectroscopy. Hetherington HP, Kuzniecky RI, Vives K, Devinsky O, Pacia S, Luciano D, Vasquez B, Haut S, Spencer DD, Pan JW. *Neurology* 2007;69(24):2256–2265. OBJECTIVE: The goal of this work was to evaluate the relationship between neuronal injury/loss in the hippocampus, thalamus, and putamen in temporal lobe epilepsy (TLE) patients using ^{1}H magnetic resonance spectroscopic imaging. METHODS: ^{1}H spectroscopic images from the hippocampus and thalamus of controls and patients with TLE were acquired at 4 T. The spectroscopic imaging data were reconstructed using an automated voxel-shifting method based on anatomic landmarks providing four, six, and three loci for the hippocampus, thalamus, and putamen, respectively. For correlation analysis, the hippocampal and striatal loci were averaged to provide single estimates of the entire structure, whereas the thalamus was divided into two regions, an anterior and posterior measure, using the average of three loci each. RESULTS: The ratio of *N*-acetyl aspartate to creatine (NAA/Cr), a measure of neuronal injury/loss, was significantly reduced in both the ipsilateral and contralateral hippocampi and thalami. NAA/Cr in the ipsilateral hippocampus was significantly correlated with the ipsilateral and contralateral anterior and posterior thalami, putamen, and contralateral hippocampus. In control subjects, the hippocampi were only correlated with each other. CONCLUSIONS: The data demonstrate that there is significant neuronal injury/loss in both the ipsilateral and contralateral thalami in temporal lobe epilepsy patients, with greater impairment in the anterior portions of the ipsilateral thalamus. The degree of injury/loss in the ipsilateral and contralateral thalamus and putamen is directly correlated with that of the ipsilateral hippocampus. This is consistent with the hypothesis that the impairment and damage associated with recurrent seizures as measured by *N*-acetyl aspartate originating in the hippocampus results in injury and impairment in other subcortical structures.

COMMENTARY

Thalamic involvement in human temporal lobe epilepsy (TLE) was first documented in 14 of 55 patients in a macroscopic and microscopic autopsy study; prospectively obtained ictal semiologies and EEGs had indicated the presence of TLE (1). Abnormalities ranged from gross atrophy to microscopic neuronal loss and gliosis. The lack of predilection to any single thalamic area suggested to the authors that retrograde degeneration from cortical destruction was not a pathogenetic factor. Of the 14 patients, hippocampal sclerosis appeared in 11 and amygdala lesions in 9.

Abundant axons extend from mesial temporal structures to the thalamus, with the medial dorsal and anterior thalamic nuclei being the principal recipients. Fibers, originating from the basolateral nuclei of the monkey amygdala, project to the magnocellular portion of the mediodorsal thalamic nucleus, while the central and medial nuclei go to midline thalamic nuclei (2). In primates, two systems connect the hippocampal region to the thalamus: 1) the mediodorsal nucleus receives afferents via the cingulum and anterior commissure, and 2) the anterior thalamic nucleus receives afferents via the fornix, mammillary bodies, and mammillothalamic tract (3–5). Projections from the entorhinal cortex extend to the pulvinar and lateral dorsal thalamic nucleus.

These abundant connections likely contribute to the reduced thalamic *N*-acetyl aspartate to creatine (NAA/Cr) ratios demonstrated in the study by Hetherington and colleagues. Although no mention of observed thalamic propagation of temporal lobe seizures could be found in the references cited in this article, thalamic ictal involvement (usually delayed) was found, using depth recordings, in 11 of 13 patients with mesial TLE in another study (6). Recovery of NAA in the nonepileptogenic temporal lobe after resection of the epileptogenic side (7) suggests that low thalamic NAA levels may reflect ictal spread and

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not simply neuronal loss—a possibility also indicated by the authors of this paper.

Results of this study suggest that thalamic dysfunction may contribute to memory impairment in some patients with medial temporal epilepsy. Lesions of the human anteromedial thalamus have long been associated with memory impairments (8). Memory deficits from mediodorsal thalamic lesions in humans resemble those of anterior mesial temporal lesions sufficiently enough to suggest a memory system involving the amygdala, the hippocampal region, and the anteromedial thalamus (9). Although thalamic lesions causing amnesia commonly involve the mediodorsal nucleus, such lesions often encompass neighboring thalamic structures. The severity of the amnesia appears to correlate with thalamic lesion size (10). The finding that NAA/Cr ratios were decreased in all thalamic areas tested in the study by Hetherington et al. (especially anterior mesial) indicates that dysfunction was amply widespread to cause or contribute to any amnesia. Note also that ratios were diminished bilaterally but asymmetrically. Among asymmetrical bilateral lesions, left- and right-accentuated ones produce primarily verbal and nonverbal memory deficits, respectively (11,12). Such bilaterality of lower NAA/Cr ratios may underlie the mixed (i.e., verbal and nonverbal) memory deficits seen in patients with unilateral temporal seizures. The lower NAA/Cr ratios found in this study are not only indicative of thalamic dysfunction but also suggest that any memory impairment in these patients would reflect more than mesial temporal pathophysiology.

Reciprocal connections between the magnocellular portion of the mediodorsal thalamic nucleus and the orbital frontal and medial frontal cortex provide a supplementary pathway to the direct pathway of temporal frontal fibers involved in ictal propagation (2). During pentylenetetrazol-induced seizures in the rat, anterior thalamus activity more closely correlated with what was occurring in the cerebral cortex than did any other thalamic nuclei to cortex activity, suggesting a greater contribution of the anterior thalamus to an ictal network (13). A matrix of calbindin-immunoreactive neurons extending throughout the primate thalamus effects synchronous, high-frequency activity with the cerebral cortex (14), which may influence coherence and ictal propagation. The various anatomical connections and physiological mechanisms described here may contribute to the presence of a generalized seizure tendency among TLE patients (15).

The correlation between NAA/Cr decreased ratios and number of seizures—but not between NAA/Cr decreased ratios and duration of the seizure disorder—found in the Hetherington et al. study is at variance with an investigation disclosing a progressive decline in human hippocampus neuronal densities that corresponded to duration of seizure disorder (16). Similarly, another study found that rat hippocampal damage correlated with "time to perfusion" and not to seizure number in a study of status epilepticus-induced epileptogenesis (17).

This study reemphasizes the role of subcortical structures in TLE. It also demonstrates that interactions between clinical and basic neuroscience are required to unravel the complexities of human epilepsy. Hopefully, technological advances will disclose point-to-point anatomical and physiological relationships between mesial temporal structures and individual thalamic nuclei.

by Warren T. Blume, MD

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Levitating Levetiracetam's Status for Status Epilepticus

Intravenous Levetiracetam in the Treatment of Benzodiazepine Refractory Status Epilepticus. Knake S, Gruener J, Hattemer K, Klein KM, Bauer S, Oertel WH, Hamer HM, Rosenow F. *J Neurol Neurosurg Psychiatry* 2008;79(5):588–589.

In 2006, levetiracetam was approved as the first of the newer anticonvulsive drugs as an intravenous formulation (ivLEV) for patients with epileptic seizures who are unable to take oral medication. We report our experience with the use of ivLEV for the treatment of 18 episodes of benzodiazepine refractory focal status epilepticus (SE) in 16 patients, including four patients with secondary generalised SE. SE was controlled in all patients by the given combination of drugs; application of further antiepileptic medications after ivLEV was necessary in two episodes. No severe side effects occurred. Our data suggest that ivLEV may be an alternative for the treatment of SE in the future, even in patients that did not respond to benzodiazepines. A large prospective, randomised, controlled study is warranted to investigate the efficacy and safety of ivLEV for the treatment of SE.

COMMENTARY

When the first intravenous (IV) medication (typically a benzodiazepine) does not stop status epilepticus (SE), administration of subsequent agents often is ineffective. In the landmark prospective, randomized clinical trial for the treatment of SE, the second agent was successful in only 7% of patients if the first agent failed (1). Although anesthetic doses of midazolam and propofol are quite effective in this situation, they frequently require respiratory support and long-term critical care. Thus, there is a need for effective IV agents that do not result in prolonged sedation or respiratory compromise. IV valproate has shown significant promise in this regard (2), and now IV levetiracetam is demonstrating similar promise.

In 2006, the United States Food and Drug Administration approved the IV formulation of levetiracetam for instances in which oral medication cannot be used: up to 1,500 mg in a single dose, administered over 15 minutes after dilution (compatible with most or all diluents). IV levetiracetam was not approved for higher doses or for use in status epilepticus. However, studies rapidly appeared showing that up to 2,500 mg over 5 minutes and up to 4,000 mg over 15 minutes could be administered safely to normal volunteers (3).

The current retrospective study by Knake et al. is the first report involving a reasonable number of patients with SE who were treated with IV levetiracetam. All patients had focal-onset SE and failed treatment with a benzodiazepine (usually lorazepam) prior to receiving IV levetiracetam. The mean levetiracetam loading dose was 944 mg, usually given over 30 minutes, followed by a mean maintenance dose of 2,166 mg/day. There were no serious adverse effects, and intubation was avoided in 17/18 episodes. Efficacy was impressive, with clinical seizure activity stopping in all patients and rarely recurring. Five patients had failed IV valproate prior to receiving IV levetiracetam; only one had failed IV phenytoin first. All patients were discharged on oral levetiracetam, with a mean dose of just over 2,000 mg/day.

The limitations of the study should be kept in mind. The group of patients was highly selective and received IV levetiracetam for SE (rather than IV phenytoin or fosphenytoin) for a particular, clinically relevant reason—most commonly because of hepatic failure or to avoid interactions with anticoagulants or chemotherapy. The study was open label and retrospective; thus, the possibility of publication bias also must be considered. Perhaps hundreds of centers have reviewed their experience with IV levetiracetam, but only those with highly impressive results go on to submit for publication. Indeed, the outcomes seem almost too good to be true. Finally, four of the eight authors have received speakers' honoraria or research grants from the manufacturer of levetiracetam, as has the author of this commentary. Nonetheless, the report by Knake et al. is quite encouraging and provides justification for future prospective clinical trials.

How does levetiracetam stop seizure activity? The mechanism remains somewhat unclear, but its study has led to interesting new insights. Levetiracetam is not effective in some of the classic animal models of acute seizures, such as maximal electroshock and pentylenetetrazol, but it is effective against several models of chronic epilepsy, such as kindling (4). This finding might suggest that it would not be effective in SE, and animal studies have been conflicting in this regard (4). Levetiracetam seems to desynchronize neuronal networks without affecting normal neuronal transmission, thereby preventing burst firing. It may prevent early changes in gene expression during kindling and modulates effects of calcium and GABA. The most interesting discovery has been that levetiracetam binds to synaptic vesicle protein 2A, a regulator of vesicular traffic and therefore, of neurotransmitter release, and the potency of binding seems to correlate with antiseizure efficacy. SV2A knockout mice have growth retardation, progressive seizures, and premature death. Exactly how levetiracetam binding to SV2A leads to decreased seizures is unclear. Some investigators have argued that IV

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levetiracetam is neuroprotective or antiepileptogenic, and there is some evidence that this is the case in models of epilepsy, stroke, trauma, and subarachnoid hemorrhage. However, there is also evidence to the contrary, as recently reviewed in this journal (5).

Does levetiracetam need to be given intravenously? The answer to this question is not clear, as oral absorption is typically excellent. However, it has not been studied in critically ill patients or those under sedation. Until the pharmacokinetics in the acute setting is known, it may be preferable to utilize IV administration during acute seizure circumstances. Having promptly available serum level determination may allow for a more rapid, yet safe switch to oral administration. There are several studies that have found oral levetiracetam (via a nasogastric tube) to be effective in acute, refractory seizures, including nonconvulsive SE (6–8).

Shortly after the current study was published, a similar study reported on the use of IV levetiracetam in 50 critically ill patients, including 24 with SE (9). SE ceased in two-thirds of the cases at a mean dose of 1,780 mg, typically given over 15–30 minutes, with seizure cessation confirmed by EEG. Two of the 50 patients given IV levetiracetam developed transient thrombocytopenia (dropping from normal to 55,000 and 82,000); no serious adverse effects were noted.

Is IV levetiracetam ready to be used routinely for the management of SE? The answer to this question is: probably not quite yet, as there have been no comparative, prospective, or randomized trials. In addition to determining its efficacy more definitively, it will be important to follow the incidence of agitation and infections in patients administered levetiracetam (IV or enterally), as both of these adverse effects are consistently more frequent for individuals on levetiracetam than on placebo in clinical trials (10), and critically ill patients are at particularly high risk for these issues. Nonetheless, IV levetiracetam has many attractive features that will ensure its common use in the inpatient setting, including: mostly renal clearance, virtually no interactions, rare allergic reactions, minimal respiratory and cardiovascular effects with IV loading, broad-spectrum efficacy, and ease of use. No other IV medication for seizures shares these features. The current report provides justification for continued use of IV levetiracetam for critically ill patients with seizures (including SE in carefully selected cases) and for assessing it in future clinical trials on the treatment of SE.

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